NINCDS, stated: "The gestations that produced the SIDS victims were characterized by a greater frequency of mothers who smoked cigarettes and had anemia" than was true for the whole population of 53,721 infants or for a set of 375 controls matched for important factors (96). Rhead, commenting on studies published to date which demonstrate an increased incidence of maternal cigarette smoking in SIDS, states: "It is now . . . clear that maternal cigarette smoking contributes to an infant's risk of dying from SIDS" (123).

Analysis of data from the prospective study of 19,047 births to members of the Kaiser Foundation Health Plan (1960–1967) also showed a strong association of SIDS with maternal smoking. In the SIDS group, 70.6 percent of mothers smoked during pregnancy, compared with only 35.3 percent of mothers of babies who did not die of SIDS ($p < .001$). The relative risk of SIDS for smokers versus nonsmokers was 4.4 (67).

Mechanisms

Clues to the mechanisms by which smoking may increase the risk of pregnancy complications are available from pathological and physiological studies of placentas, membranes, blood vessels, circulatory patterns, and serum levels of substances important for cell and tissue integrity. For example, it is possible that placental changes in smokers that serve as adaptations to the hypoxic effects of carbon monoxide may also increase the risk of placental complications.

Christianson has reported findings from carefully standardized gross examinations of 7,651 placentas from smokers and nonsmokers. These examinations revealed that smokers' placentas were thinner and larger in their minimum diameter than those of nonsmokers. This significant change effectively increased the surface area of the smokers' placentas and must, therefore, have increased their area of attachment to the uterine wall. The distance from the edge of membrane rupture to the placental margin was also less for smokers, and significantly more smokers than nonsmokers had zero distance, which is consistent with the diagnosis of placenta previa (19). These findings suggest a possible mechanism to account for the significant dose-related increase in the frequency of the clinical diagnosis of placenta previa that accompanies maternal smoking (86). A similar increase in this condition occurs with increasing altitude (75).

Christianson's study also revealed that smokers had significantly more placental calcification, primarily of the maternal surface, and patchy subchorionic fibrin, as shown in Table 11.

TABLE 11.—Selected results of gross examinations of placentas from smokers and nonsmokers

	Percent of Placentas with Stated Condition					
	White			Black		
	Nonsmoker N=3,461	Smoker N=2,239	P	Nonsmoker N=1,300	Smoker N=652	P
Calcification	49.5	60.8	<.0001	43.5	59.0	<.0001
Patchy Subchorionic Fibrin	26.2	35.3	<.0001	30.8	37.0	<.01
Infarcts	24.6	22.3	<.05	14.4	14.5	NS
Thickness (mean cm)	2.16	2.12	<.001	2.11	2.06	<.01
Ratio of smallest diameter to thickness	8.19	8.40	<.001	8.39	8.68	<.01
Shortest distance, edge of rupture of membranes to placental margin (mean cm)	4.32	4.09	<.025	5.08	4.83	NS
Percent with zero distance	25.6	27.9	NS	18.6	20.3	<.05

SOURCE: Christianson, R.E. (19).

These changes are characteristic of maturation and aging of the placenta and occur as normal gestation proceeds; however, they occurred earlier in smokers than in nonsmokers (19). This finding is compatible with other manifestations of accelerated aging reported to be associated with cigarette smoking (28,108).

Asmussen compared placental vessels in smoking and nonsmoking mothers by electron microscopy. In the smoking group these vessels were characterized by subintimal edema with destruction of the intimal elastic membranes, a marked decrease in collagen content, and proliferation of myocytes. Asmussen postulated that similar damage may occur in the fetal and infant vascular system. To what extent such changes may predispose to the subsequent development of vascular disease remains unknown. The author regarded most of the changes observed in smokers' vessels as degenerative, but mentioned the possibility that the thickening of the basement membrane observed in smokers might be an attempt at repair (4,5). Naeye (93) has described an increased frequency of placental microscopic lesions associated with smoking. These include: cytotrophoblastic hyperplasia, obliterative endarteritis, stromal fibrosis, and small villous infarction. Smokers also demonstrated an increased frequency of necrosis and inflammation in the decidua capsularis and in the decidua basalis at the placental margin. Placental features observed less frequently in smokers' placentas were excessive syncytial knots and various thrombotic phenomena.

Naeye found increasing placental enlargement with smoking level, accompanied by decreasing birth weight and a consequent increase in the placental ratio. The author stated that "as smoking increased, placentas developed microscopic lesions characteristic of underperfusion of the uterus." Naeye's data showed positive trends with maternal smoking level for some findings and negative trends for others (93). Many of the changes cited were of low frequency in all groups, and no clear pattern of possible mechanisms of action emerged.

Other studies that may shed light on these complex interrelationships include the report by Goujard and colleagues that heavy alcohol consumption as well as smoking contributes to the risk of stillbirth caused by abruptio placentae. In a prospective survey of 9,169 women, the risk of stillbirth was 21 per 1,000 in smokers who were light or nondrinkers, 20 per 1,000 in nonsmoking drinkers of 45 ml equivalents or more of absolute alcohol per day, and 8.5 per thousand for nonsmokers who drank less than 45 ml per day. The small number of smokers who were also heavy drinkers had stillbirth rates of 50.5 per 1,000 (95 women with 5 stillbirths). The proportions of these deaths that were attributable to abruptio placentae increased with smoking and with drinking, based on data unadjusted for the effects of age, parity, and other factors (122).

More research is needed to define possible pathways of action by which the active components of cigarette smoke affect pregnancy complications that may lead, in turn, to fetal death or to preterm birth with or without survival.

Experimental Studies

TOBACCO SMOKE

Tobacco smoke contains more than 2,000 compounds including: carbon monoxide, oxides of nitrogen, ammonia, polycyclic aromatic hydrocarbons, hydrogen cyanide, vinyl chloride, and nicotine. For the pregnant woman and fetus the most important of these appear to be nicotine, carbon monoxide, and the polycyclic aromatic hydrocarbons.

NICOTINE

The effect of nicotine on sympathetic and parasympathetic ganglia, skeletal muscles, and the central nervous system is similar to that of acetylcholine. At all three sites it first stimulates, then depresses. Minute doses of nicotine stimulate the chemoreceptors of the carotid and aortic bodies, causing reflex hypertension. Nicotine also releases epinephrine from the adrenal medulla, thereby producing cardiovascular changes. Thus, it can produce widely differing effects depending upon the dosage and the particular site that is most sensitive to stimulation.

Nicotine rapidly crosses the placenta to affect the fetus (142). Relatively mature rhesus monkey fetuses respond to nicotine infusion with a rise in blood pressure, bradycardia, acidosis, hypercarbia, and hypoxia (141). Maternal nicotine administration in rats also has been shown to affect the fetal central nervous system and its response to electrical stimulation during the newborn period (56,78).

Quigley, et al. noted that in moderate to heavy smokers, after 34 weeks gestation, smoking two cigarettes in 10 minutes was associated with a 60 percent increase in maternal plasma norepinephrine and epinephrine and a 20 percent increase in serum cortisol concentrations (118). These changes also were associated with an increase in maternal pulse and blood pressure. Lehtovirta and Forss measured changes in placental intervillous blood flow using the 133 xenon method (66). Immediately after smoking, intervillous flow decreased 22 percent.

These data correlate with the studies of Resnik, et al. (122), showing nicotine-induced increases in catecholamines and decreased uterine blood flow in sheep, and of Haberman, demonstrating decreased uteroplacental blood flow in women, using thermography (48).

Sastry and his colleagues have carried out a series of studies on the effect of nicotine on the human placenta. Nicotine added to a calcium-containing medium caused a 33 percent increase in the rate of acetylcholine release from isolated placental villi (131). The authors postulated that this effect could account for the decrease in placental amino acid transport (125,154) produced by nicotine-mediated cholinergic blockade (105). Rowell and Sastry also demonstrated that nicotine caused a 41 percent decrease in uptake of alpha amino isobutyric acid in an experimental placental system (126). Their studies indicate that under normal circumstances acetylcholine exhibits a muscarinic effect facilitating placental amino acid uptake. Nicotine blockade of the facilitating effects of acetylcholine on amino acid uptake may result in fetal growth retardation (126). These data agree with the 1977 work of Crosby, et al. in humans (26).

Nicotine injection in rats results in prolonged gestation with lower than normal newborn weights. A possible cause of this prolonged gestation is nicotine-induced delay in ovum implantation. Yoshinaga, et al. tested this hypothesis, administering 7.5 mg nicotine tartrate twice daily from the morning of proestrus until the day of sacrifice on days 1 to 5 of pregnancy (161). The nicotine-injected animals demonstrated a delay of about 12 hours in ovum cleavage from the two- to the four-cell stage, and each step of development after the four-cell stage was thereby delayed. In addition, ovum entry into the uterus, blastocyst formation, shedding of the zona pellucida, and implantation were delayed. Nicotine injection also was associated with a "crowding" of implantation sites toward the tubal ends of the uterine horns.

During the preimplantation period the serum concentrations of progesterone, luteinizing hormone, and prolactin were lower, while the concentrations of estrogen and follicle stimulating hormone were higher than in control animals. These workers suggested that the delayed ovum implanation followed a delayed increase in progesterone secretion required to prepare the uterus for the implanting blastocyst, and that the delayed progesterone secretion results in part from nicotine-induced disturbed hypothalamus pituitary balance.

Hamosh, et al. observed that, while administration of 100 mg $kg^{-1}day^{-1}$ nicotine to pregnant rats from day 14 gestation onward failed to affect the mother or fetus, administration of 1 mg $kg^{-1}day^{-1}$

(a dose "comparable" to that of a 20 cigarette-per-day smoker) resulted in a decrease in litter size and an increase in stillbirth rate. Although administration of 100 mg $kg^{-1}day^{-1}$ nicotine failed to affect newborn birth weight by 12 days of age continued maternal nicotine administration resulted in a 9 percent decrease in body weight and a 40 percent decrease in weight of the stomach contents. These decreases presumably resulted from lower milk production by the nicotine-treated animals (51).

CARBON MONOXIDE (CO)

Carboxyhemoglobin concentrations of 4 to 5 percent are associated with numerous physiologic alterations in adults. Cigarette smoking raises the carboxyhemoglobin concentration 4 to 5 percent per pack smoked per day. Although CO diffuses across the placenta relatively slowly [the half time equals 1.5 to 2 hr (72)], fetal carboxyhemoglobin concentrations reflect those of the mother, and under steady state conditions are 10 to 15 percent higher than maternal levels (71). Elevated carboxyhemoglobin concentrations in the fetus are associated with decreased fetal blood oxygen tensions. These decreased oxygen tensions are associated with a redistribution of fetal blood flow to the brain, heart, and adrenal glands (146).

Carboxyhemoglobin concentrations have been described under several conditions of pregnancy. Davies, et al. (31) compared carboxyhemoglobin concentrations and "available oxygen" (a function of O_2 content in ml dl $blood^{-1}$) in women who stopped smoking for 48 hours during the last trimester of pregnancy, with women who did not stop smoking, and with nonsmoking women. In those women who stopped smoking, carboxyhemoglobin concentrations decreased. "Available oxygen" increased about 8 percent due both to an increase in functioning hemoglobin and a shift in the oxyhemoglobin saturation curve; this increase in "available oxygen" should contribute to improved fetal oxygenation.

Exposure of rabbits (6) and rats (39) to CO during gestation resulted in decreased fetal weights and increased perinatal mortality. Such CO-exposed newborn animals showed less activity as well as decreased lung weights and decreased concentrations of brain protein, DNA, and the neurotransmitters norepinephrine and serotonin (45). Cellular hypoxia is the final common pathway mediating the adverse effect of CO on the developing fetus.

Recent experimental studies have explored various aspects of CO-induced biochemical changes in the fetus and the newborn. Newby, et al. demonstrated a persistent effect of CO exposure in 8- and 13-day-old rats following a single 5-hour exposure to 1,500

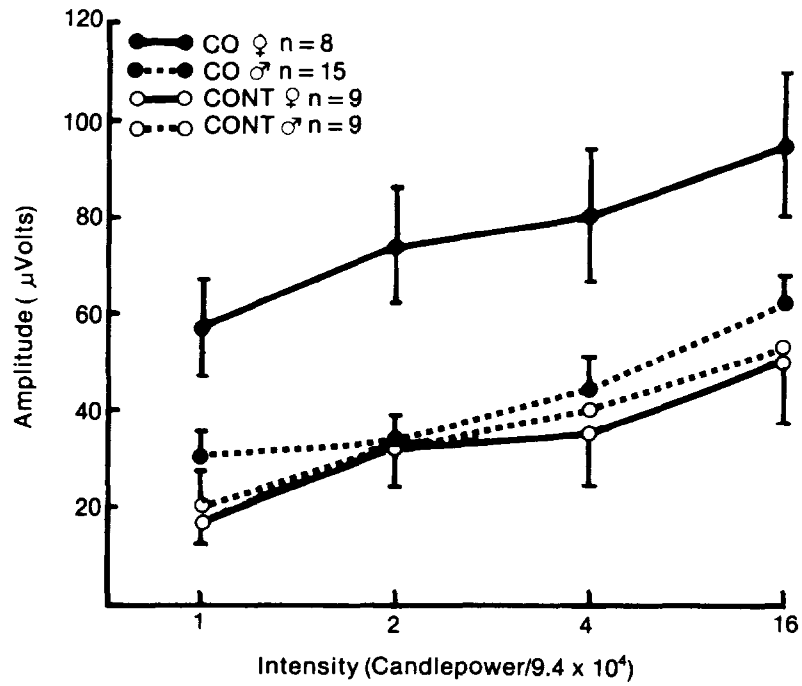

FIGURE 12.—Effect of prenatal CO upon peak-to-peak amplitudes of the first positiive to the first negative component of the flash evoked potential recorded from the rat visual cortex. Vertical bars represent ± standard error of the means

SOURCE: Dyer, R.S. (36).

parts per million (0.15 percent CO) (100). In these animals alpha methyl-p-tyrosine, a potent inhibitor of the enzyme tyrosine hydroxylase, was injected 1 hour before the CO exposure, and the extent of catecholamine depletion was taken as an index of the rate of catecholamine turnover. CO-treated rats showed increased steady state dopamine concentrations with decreased rates of dopamine turnover. In addition, the CO effect on dopamine turnover persisted for at least 3 to 6 weeks after a single exposure of 8-day-old rats. There was no CO effect on norepinephrine concentrations or turnover rates, and the effect was not produced in rats exposed to 8 percent oxygen instead of carbon monoxide. This is consistent with the data of Coyle and Campochiaro, which indicates that a maturational event occurs in the striatum of the 8-day-old rat (25). Whether this event represents the age of functional maturity, initiation of dopaminergic transmission, or maturation of cholinergic interneurons is unclear.

Prenatal CO exposure may have long-term consequences on central nervous system function. For instance, Dyer, et al. exposed female Long-Evans hooded rats to 150 ppm CO throughout pregnancy (36). At birth the litters and mothers were placed in room air without CO. On day 65 electrodes were placed in the young rats' skulls, and 2 weeks later visually evoked potentials were recorded. Figure 12 illustrates the effect of such prenatal exposure on the peak-to-peak amplitudes of the P1-N1 (first positive to first negative) component of the visual evoked potential from the cortex. Females showed a significant increase in P1-N1 amplitude at each of four flash intensities. Although the exact nature of this amplitude increase could not be determined, it suggests altered cell populations at the retinal, geniculate, and cortical levels, and may represent impaired inhibitory mechanisms, rendering other neurons more excitable.

The question of the posible teratogenicity of CO has never been resolved. Schwetz, et al. exposed mice to 250 ppm CO for 7 or 24 hours per day, from days 6 through 15 of gestation, and rabbits to the same concentration from days 6 through 18 (137). Blood carboxyhemoglobin concentration ranged from 10 to 15 percent. The fetuses of mice exposed to CO for 7 and 24 hours per day were slightly heavier and lighter, respectively, than those of the control animals. The only increase in teratogenic effects were minor skeletal variants such as extra lumbar ribs and spurs.

POLYCYCLIC AROMATIC HYDROCARBONS

The polycyclic aromatic hydrocarbons (PAH), such as benzo(a)pyrene, are widely distributed mutagens and carcinogens. These substances, produced by incomplete combustion of organic material, are important constituents of tobacco smoke. Exposure of cells to PAH induces the enzyme, aryl hydrocarbon hydroxylase. The inducibility of this enzyme system has been used by some workers to demonstrate, indirectly, that benzo(a)pyrene and other polycyclic hydrocarbons reach the placenta and fetus.

The placental concentration of benzo(a)pyrene is highly correlated with the amount which a pregnant woman smokes (97, 111). In pregnant rats exposed to this substance higher doses were required to induce enzyme activity in the fetus as compared with the dose required to stimulate placental enzyme activity (153), suggesting that the placenta may protect the fetus from these substances. However, the placenta is not impermeable to benzo(a)pyrene (134). The placenta is involved in complex hormonal interrelations between mother and fetus, and oxidative enzyme pathways in the placenta are important in maintaining hormonal and nutrient balance for normal fetal development. The hydroxylation of polycyclic hydrocarbons and the active transport of various compounds by trophoblast cells may share common enzyme systems. Thus, the induction of various enzymes by polycyclic hydrocarbons may interfere with normal transport systems.

Another unanswered question concerns the carcinogenic risk for progeny exposed *in utero* to polycyclic aromatic hydrocarbons. The offspring of mice that were injected with benzo(a)pyrene late in gestation showed an increased incidence of neoplasms of the lungs, liver, and mammary glands (101). Pelkonen, et al. determined that placental aryl hydrocarbon hydroxylase activity correlated closely with both the amount the mother smoked and newborn weight (112). These authors suggested that the placental concentration of this enzyme may be used as a measure of fetal exposure to maternal cigarette smoking. Vaught, et al. also reported much higher aryl hydrocarbon hydroxylase activity in the placental microsomes of smokers compared with nonsmokers (148).

Although currently available data do not allow a quantitative assessment of the genetic risk to man from cigarette smoking, such risk may occur since so many components of cigarette smoke are mutagens (as well as carcinogens) (11). Male cigarette smokers may have an increased number of abnormal spermatozoa (150). Paternal and maternal chromosomal aberrations (103) and sister chromatid exchanges may be increased in smokers (62). Because the proportion of smokers in the population is so high (between 30 and 50 percent), even a relatively weak mutagenic effect could have a significant effect on the gene pool (11).

OTHER COMPONENTS

Cyanide, another constituent of cigarette smoke, may contribute to retarded infant growth and increased perinatal mortality. Smokers have increased levels of cyanide and thiocyanate in body fluids. Serum concentrations of vitamin B_{12}, used in cyanide metabolism, are decreased as well. Several workers have recorded increased thiocyanate concentrations in both women who smoke and in their fetuses (2,140,154). Pettigrew, et al. compared cyanide and thiocyanate concentrations in smokers and nonsmokers, matched for age, height, parity, and socioeconomic status (116). Cyanide and thiocyanate concentrations were two to four times greater in the blood and urine of smokers and in the urine of smokers' infants as compared with controls. Meberg, et al. reported that thiocyanate concentrations were correlated with cigarette consumption and inversely correlated with birth weight (81).

Cadmium, another constituent of tobacco smoke, is concentrated in the placenta of smokers (124). Webster exposed pregnant mice to 10 to 40 ppm cadmium and noted an inverse correlation between cadmium concentration and fetal weight (152).

Lauwerys, et al. examined the effects of epidemiology factors on heavy metal and CO concentrations in the blood, placenta, and fetus of smoking women (65). Cadmium concentrations in maternal blood were twofold greater than concentrations in fetal blood, suggesting that the placenta acts as a barrier to this metal. They reported a correlation between maternal cadmium and carboxyhemoglobin concentrations (13,65). They also found that the cadmium concentration of smokers' placentas was about 25 percent greater than in a control group and that the placental cadmium concentration exceeded that of maternal blood about tenfold (124).

Fertility

Fertility results from the successful completion of a complex step-wise process beginning with gametogenesis (sperm and egg production), continuing through gamete release (ejaculation and ovaluation), gamete interaction (fertilization), conceptus transport through the fallopian tube into the uterus, and ending with implantation of the embyro into the endometrial wall. An adverse effect of smoking on any of these steps may impair fertility.

SMOKING AND REPRODUCTION IN WOMEN

Several epidemiologic studies have suggested that smoking decreases fertility in women (50,115,143,149). The retrospective study of Tokuhata demonstrated that 21 percent of women who regularly smoked cigarettes were infertile while only 14 percent of those who never used tobacco regularly were infertile (143). After several characteristics (cause of death, age at and year of death, education, occupation and frequency of marriage as well as husbands' smoking habits, education and occupation) were controlled, a 46 percent excess of infertility was found in women who smoked.

In a study on the return of fertility after discontinuing contraception, Vessey, et al. found a suggested reduction in fertility among women smoking 15 or more cigarettes per day (149). Pettersson, et al. found a tendency toward a greater prevalence of secondary amenorrhea among smokers (4.8/100 women) than among nonsmokers (3.7/100 women) (115). Hammond found that 49 percent of the nonsmoking women between 40 and 49 years had regular menses while only 40 percent of those smoking more than one pack a day had a regular menses (50). Conversely only 18 percent of nonsmokers had irregular menses while 24 percent of those smoking one or more packs of cigarettes per day said they had irregular menses. Smoking women were also more likely to have an unusual vaginal discharge and vaginal bleeding than nonsmokers. Experimental studies have demonstrated alterations in luteinizing hormone release and a decreased ovulatory response in rats exposed to tobacco smoke (76).

The effect of smoking on ovulation may result from direct effects of nicotine on the hypothalamus or pituitary. This would alter the release of gonadotropin releasing hormones from the hypothalamus or impair the pituitary response to releasing hormones.

SMOKING AND AGE OF MENOPAUSE

Substantial data demonstrate that smoking lowers the age of spontaneous menopause (7,9,27,58,68,69). The recent study by Jick, et al. revealed a dose dependent decrease in the age of menopause in smoking women who live in Sweden and the United States (58). The median age of menopause in nonsmokers was 50; among those smoking one-half pack/day it was 49; in those smoking 1 or more pack/day, it was 48. Similar studies have been published indicating an earlier onset of menopause in smoking women in the United States (29), in England (7), in Germany (9), and in Sweden (68,69). The mechanism of early menopause in smokers may be related to ovotoxins in cigarette smoke (37) or to toxic alterations in the hormonal regulatory mechanisms controlling the hypothalamic-pituitary-ovarian axis (76). One group of ovotoxins may be polycyclic aromatic hydrocarbons which have been demonstrated to be metabolized by ovarian enzymes to toxic products which destroy oocytes in rat and mouse ovaries (47,79).

Evidence collected by Daniell (29) and Lindquist (68) suggest that the earlier menopause of smokers is not related to weight differences between smokers and nonsmokers but is a direct result of some component of cigarette smoke.

SMOKING AND REPRODUCTION IN MEN

Spermatogenesis, sperm morphology, sperm motility (17,64,133,150) and androgen secretion (12,113) appear to be altered in men who smoke. Viczian (150) has demonstrated decreased sperm density, a cigarette-dose-dependent decrease in sperm motility, and a cigarette-dose-dependent increased abnormal sperm morphology among smokers.

In metabolic studies of alcoholic men admitted to a clinical research center, an inverse relationship between number of cigarettes smoked and reduction of testosterone levels was seen (113). Briggs (12) has reported lower plasma testosterone among smoking men compared to matched nonsmoking controls and has shown that cessation of smoking resulted in increased testosterone levels in these men. Wintermitz and Quillen (158) in a study on the acute effects of smoking in men demonstrated increases in plasma cortisol and growth hormone during the smoking period. Growth hormone returned to the presmoking level shortly after the smoking period, and cortisol fell gradually to the presmoking level by 90 minutes after cessation of smoking. Urinary catecholamines were higher on the smoking day than the nonsmoking day. No acute changes were observed in gonadotropins or testosterone in these men. These studies demonstrate stimulatory effects of smoking on growth hormone and cortisol.

Studies in experimental animals have also shown that tobacco smoke impairs spermatogenesis (37,151). Smoking also lowers sexual activity in male rats (18).

These data suggest two possible mechanisms of action of smoking on male reproduction. A component of cigarette smoke may have a direct action on the testes, disrupting gamete production. This would be consistent with the suggested effect of cigarette smoke on the ovary. In addition, cigarette smoke is known to contain compounds which are mutagenic (59). Alternatively, cigarette smoke may interfere with the regulatory mechanisms controlling the hypothalamic–pituitary–testicular axis.

FERTILIZATION AND CONCEPTUS TRANSPORT

The effect of smoking on sperm-egg interaction (fertilization) has not been studied in mammalian species. Evidence from sub-mammalian species demonstrates that nicotine promotes polyspermy (the entrance of more than one sperm into the oocyte) (73). Polyspermy would result in abnormal embryonic development and early abortion, which is one known effect of smoking (60).

The effect of smoking on conceptus transport in the fallopian tube or entry into the uterus is unknown; however, some evidence suggests that smoking can alter the amplitude and tone of contractions measured during the Rubin uterotubal insufflation test (a combined measure of uterotubal junction and tubal patency) (98), suggestive that smoking may alter conceptus transport in the fallopian tube or its entrance into the uterus.

In summary, cigarette smoking appears to exert an adverse effect on fertility. Further studies are needed to quantify the effects, identify etiologic agent(s), and define the mechanism(s) of action.

Summary

1. Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable nonsmoking women.
2. The relationship between maternal smoking and reduced birth weight is independent of all other factors that influence birth weight including race, parity, maternal size, socioeconomic status, and sex of child; it is also independent of gestational age.
3. There is a dose-response relationship between maternal smoking and reduced birth weight; the more the woman smokes during pregnancy, the greater the reduction in birth weight.
4. If a woman gives up smoking early during pregnancy, her risk of delivering a low-birth-weight baby approaches that of a nonsmoker.
5. The ratio of placental weight to birth weight increases with increasing levels of maternal smoking, reflecting a considerable decrease in mean birth weight and a slight increase in mean placental mass; this may represent an adaptation to relative fetal hypoxia.
6. The pattern of fetal growth retardation that occurs with maternal smoking is a decrease in all dimensions including body length, chest circumference, and head circumference.
7. Maternal smoking during pregnancy may adversely affect the child's long-term growth, intellectual development, and behavioral characteristics.
8. Maternal smoking during pregnancy exerts a direct growth-retarding effect on the fetus; this effect does not appear to be mediated by reduced maternal appetite, eating or weight gain.
9. The risk of spontaneous abortion, fetal death, and neonatal death increases directly with increasing levels of maternal smoking during pregnancy; interaction of maternal smoking with other factors which increase perinatal mortality may result in an even greater risk.
10. Excess deaths of smokers' infants are found mainly in the coded cause categories of "unknown" and "anoxia" for fetal

deaths, and the categories of "prematurity alone" and "respiratory difficulty" for neonatal deaths; this suggests that the excess deaths are due to problems of the pregnancy, rather than to abnormalities of the fetus or neonate.

11. Increasing levels of maternal smoking result in a highly significant increase in the risk of abruptio placentae, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery—all of which carry high risks of perinatal loss.

12. Although there is little effect of maternal smoking on mean gestation, the proportion of fetal deaths and live births that occur before term increases directly with maternal smoking level. Up to 14 percent of all preterm deliveries in the United States may be attributable to maternal smoking.

13. The incidence of preeclampsia is decreased among women who smoke during pregnancy; however, if preeclampsia develops in a smoking woman, the risk of perinatal mortality is markedly increased compared to preeclamptic nonsmokers.

14. An infant's risk of developing the "sudden infant death syndrome" is increased by maternal smoking during pregnancy.

15. There are insufficient data to support a judgement on whether maternal and/or paternal cigarette smoking increases the risk of congenital malformations.

16. Infants and children born to smoking mothers may experience more long-term morbidity than those born to nonsmoking mothers; however, studies usually cannot distinguish between the effects of smoking during pregnancy and the effects of the infant's or child's passive exposure to cigarette smoke after birth.

17. Studies in women and men suggest that cigarette smoking may impair fertility.

18. Experimental studies on tobacco smoke, nicotine, carbon monoxide, polynuclear aromatic hydrocarbons, and other constituents of smoke help define pathways by which maternal smoking during pregnancy may exert its aforementioned effects.

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